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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07H 15/18, 13/04, 3/06

A1

(11) International Publication Number: WO 95/08553

(43) International Publication Date: 30 March 1995 (30.03.95)

(21) International Application Number: PCT/US94/10790

(22) International Filing Date: 22 September 1994 (22.09.94)

(30) Priority Data:
08/125,592 22 September 1993 (22.09.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/125,592 (CIP)
Filed on 22 September 1993 (22.09.93)

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(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYNTHESIS OF SELECTIN LIGANDS

(57) Abstract

The total synthesis of the naturally occurring sulfated Le^x and Le^a tetrasaccharides, trisaccharide analogs of sulfated Le^x and Le^a, and multivalent Le^x selectin ligands are described.

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SYNTHESIS OF SELECTIN LIGANDS

Specification

Field of Invention:

The invention relates to the total syntheses of the naturally occurring sulfated Le^x and Le^a tetrasaccharides and related compounds. More particularly, the invention relates to compounds which are truncated analogs of sulfated Le^x and Le^a, to key intermediates in the synthesis of sulfated Le^x and Le^a tetrasaccharides and related compounds and to multivalent Le^x selectin ligands.

Background of the Invention:

Sialyl Lex-type molecules serve as ligands to E-selectin and contribute to the recruitment of leukocytes to inflammation sites. Several investigators contributed to the initial identification of sialyl Lex-type molecules as ligands to E-selectin, e.g., M. Bevilacqua et al. (*Science* **1989**, *243*, 1160), J. Lowe et al. (*Cell* **1990**, *63*, 475), M. Phillips et al. (*Science* **1990**, *250*, 1130), G. Walz et al. (*Science* **1990**, *250*, 1132) and M. Tiemeyer et al. (*Proc. Natl. Acad. Sci., USA* **1991**, *88*, 1138). The chemistry and biology of selectins with respect to the recruitment of leukocytes to inflammation sites via vascular adhesion and rolling have been elegantly characterized by L. Lasky (*Nature* **1991**, *349*, 196 and *Science* **1992**, *258*, 964), by S. Borman (*Chem. & Eng. News* 1992, *70* (49), 25) and by J. Travis (*Science* **1993**, *260*, 906).

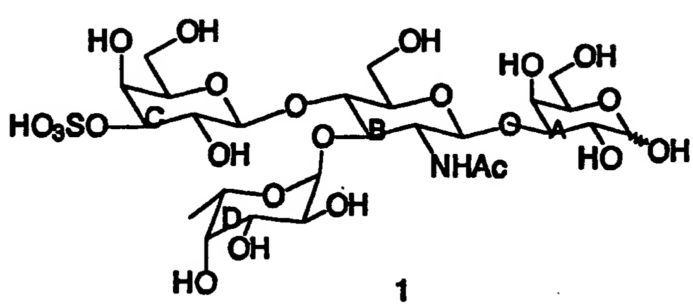
More recently, C.-T. Yuen et al. (*Biochem.* **1992**, *31*, 9126) disclosed the isolation of a mixture of two sulfated tetrasaccharides from an ovarian cystadenoma glycoprotein, i.e., sulfated Le^x and sulfated Le^a.

These sulfated compounds exhibited E-selectin binding properties comparable to those of the sialylated compound, e.g. sialyl Lex. Due to the importance of these ligands to adhesion processes and their extreme scarcity, their synthesis has been deemed important and has received considerable attention. Methods for the synthesis of sialyl Le^x compounds have been disclosed by several workers, e.g., M. Palcic et al. (*Carbohydr. Res.* 1989, *190*, 1), D. Dumas et al. (*Bioorg. Med. Chem. Lett.* 1991, *1*, 425), A. Kameyama et al. (*Carbohydr. Res.* 1991, *209*, C1), K.C. Nicolaou et al. (*J. Am. Chem. Soc.* 1992, *114*, 3126), S. Danishefsky (*J. Am. Chem. Soc.* 1992, *114*, 8329 and *J. Am. Chem. Soc.* 1992, *114*, 8331), and Y. Ichikawa (*J. Am. Chem. Soc.* 1992, *114*, 9283).

However, sulfated forms of Le^x and of Le^a reported by C.-T. Yuen (supra) have not been disclosed. Given the biological importance of these sulfated molecules and their relative scarcity, there was a great need for a synthetic method for producing such compounds and their analogs.

<u>Summary</u>:

The invention relates to the synthesis of sulfated Le^x-type tetrasaccharides. More particularly, the invention is the total syntheses of sulfated Le^x 1 and of sulfated Le^a 2 and related



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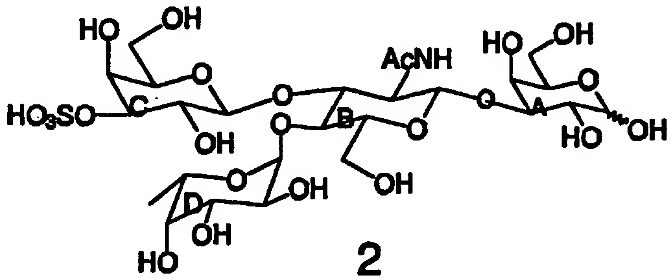

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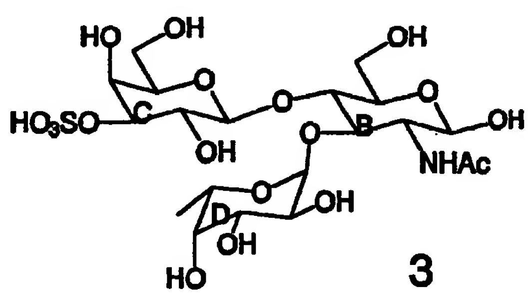
compounds. Compounds 1 and 2 are tetrameric carbohydrates having four rings, viz. ring A, ring B, ring C, and ring D. The invention includes the synthesis of truncated analogs of sulfated Le^x 1 and sulfated Le^a 2 such as compounds 3 and 4, indicated below. Compound 3 is a truncated version of Le^x 1 and compound 4 is a truncated version of Le^a 2. The truncated compounds 3 and 4 lack ring A. The invention also includes various key intermediates employed in the syntheses of sulfated Le^x 1 and of sulfated Le^a 2, i.e., compounds 5 - 10 and includes multivalent Le^x selectin legands. Compounds 1 - 4 and 5 - 10 are illustrated in Fig. 1.



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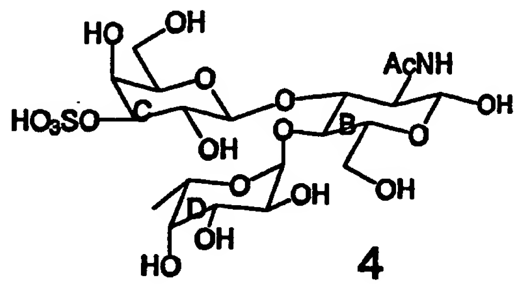

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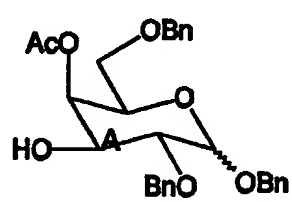
Synthesis of Sulfated Le^x-type Tetrasaccharide 1:

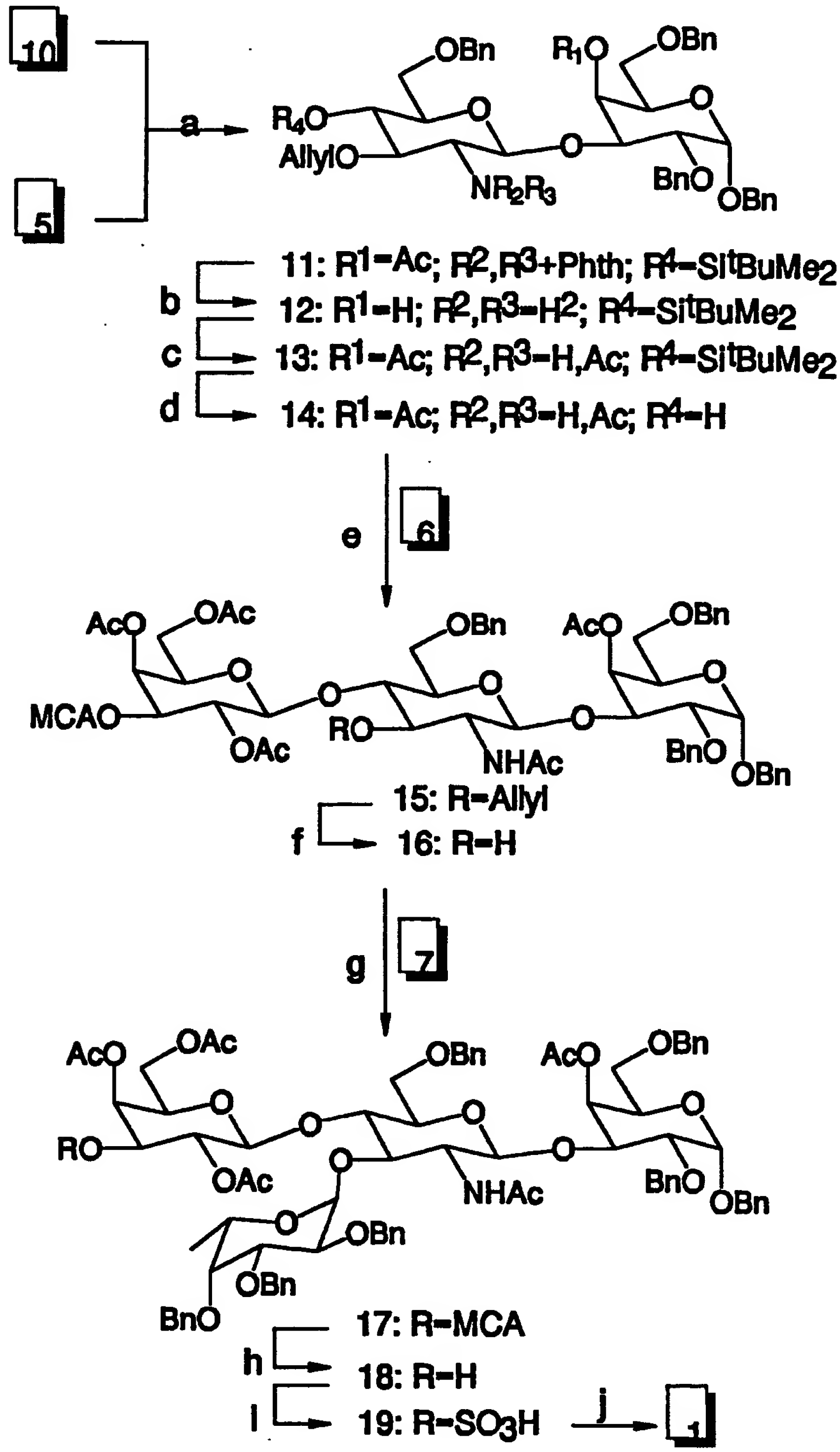
The synthesis of the sulfated Le^x-type tetrasaccharide 1 is summarized in Scheme I. The glycosyl donor 10 is coupled with the glycosyl acceptor 5 under standard Mukaiyama conditions, i.e., $AgClO_4$-$SnCl_2$ (T. Mukaiyama et al., *Chem. Lett.* 1981, 431). The resultant glycoside 11 is stereoselectively β-linked and is produced with a 90% yield. The precise chemical mechanism ccounting for the stereoselectivity of this glycoside bond ormation is unknown but presumed to involve the participation of the neighboring group. Treatment of glycoside 11 with $MeNHNH_2$ in refluxing ethanol resulted in removal of both the acetate and the phthalimide groups leads to the corresponding amino alcohol,

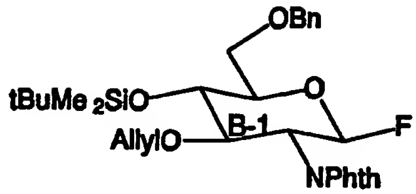


[from D-galactose]

5

Scheme I a


10
5
a
OBn
R1O
OBn
R4O
AllylO
NR2R3
BnO
OBn
11: R1=Ac; R2,R3+Phth; R4=SitBuMe2
b
12: R1=H; R2,R3=H2; R4=SitBuMe2
c
13: R1=Ac; R2,R3=H,Ac; R4=SitBuMe2
d
14: R1=Ac; R2,R3=H,Ac; R4=H
e
6
AcO
OAc
OBn
AcO
OBn
MCAO
OAc
RO
NHAc
BnO
OBn
15: R=Allyl
f
16: R=H
g
7
AcO
OAc
OBn
AcO
OBn
RO
OAc
NHAc
BnO
OBn
OBn
OBn
BnO
17: R=MCA
h
18: R=H
i
19: R=SO3H
j
1



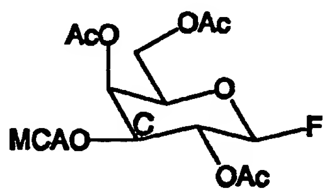
[from D-glucosamine]

10

i.e., compound **12**. Compound **12** may then be acetylated to give the amide **13** with an overall yield of 80%. Desilylation of amide **13** using fluoride ion leads to hydroxy compound **14** with a yield of 95%. Hydroxyl compound **14** may then be coupled with the galactosyl fluoride **6** to furnish the trisaccharide **15** as a single stereoisomer with a yield of 75%. (See Mukaiyama, supra) The synthesis of galactosyl fluoride **6** is shown in Scheme VI. Selective removal of the allyl protecting group from trisaccharide **15**, i.e., $H_2Ru(PPh_3)_4$ followed by acid hydrolysis, gives the hydroxy compound **16** with a yield of 81%. The hydroxyl compound **16** may then be coupled with the fucosyl fluoride derivative **7** ($AgClO4-SnCl2$) by the method of K.C. Nicolaou et al., (*J. Am. Chem. Soc.* **1990**, *112*, 3693) to give, stereoselectively, tetrasaccharide **17** with the desired α-fucose anomeric linkage with a yield of 85%. Reaction of tetrasaccharide **17** with thiourea leads to selective removal of the chloroacetyl group to afford alcohol **18** with a yield of 81%. In turn, alcohol **18** may be converted to the sulfated compound **19**, in 95% yield, by exposure to $SO_3 \cdot NMe_3$ complex in anhydrous pyridine. Finally, deacetylation of compound **19** followed by hydrogenolysis gives the targeted sulfated Le^x tetrasaccharide **1** in 80% overall yield.

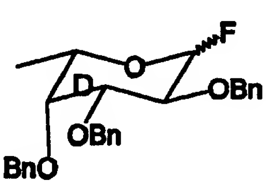
Synthesis of Truncated Sulfated Le^x-type Trisaccharide 3:

The synthesis of the sulfated derivative 3 lacking the galactose unit at the reducing end may be accomplished as depicted in Scheme II using the carbohydrate units 6, 7, and 9 and similar chemistry as described above. Synthesis of carbohydrate unit 9 is described by K.C. Nicolaou et al. (*J. Chem. Soc., Chem. Commun.* 1991, 870). It is interesting to note that an earlier synthesis of compound 3 by E. Chandrasekaran et al. (*J. Biol. Chem.* 1992, 267, 23806) was reported prior to the actual elucidation of the natural products, i.e., the sulfated Le^x (1) and sulfated Le^a (2).



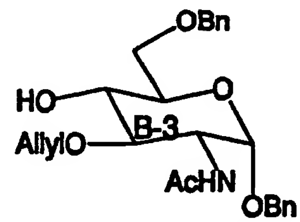
[from D-galactose]

6



[from L-fucose]

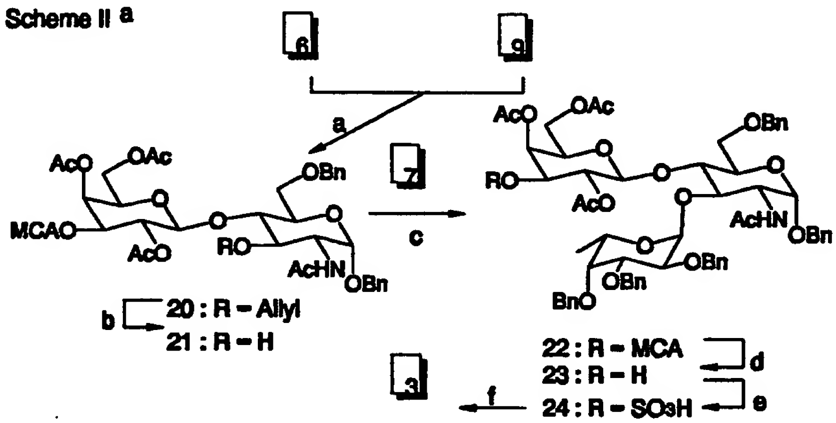
7



[from D-glucosamine]

9

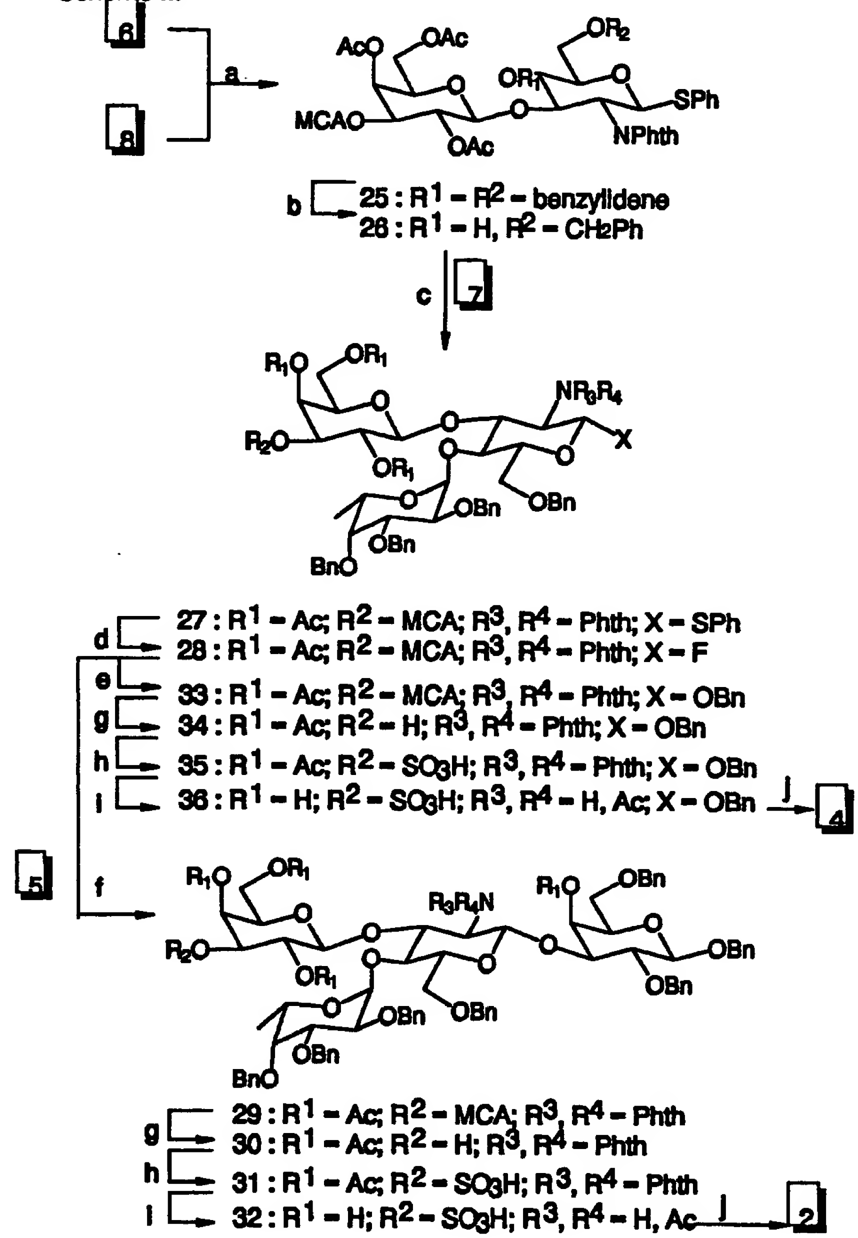
Scheme II a



<u>Synthesis of sulfated Le^a-type compounds 2 and 4</u>

Employing the strategy outlined above for synthesizing sulfated Le^x can not be employed for synthesizing sulfated Le^a. An attempt to do so led to unexpected glycosidation problems. Accordingly, we developed a different strategy for the synthesis of the sulfated Le^a-type compounds **2** and **4**. Scheme III summarizes the successful routes to compounds **2** and **4**. Thus, coupling of carbohydrate units **6** and **8** under Mukaiyama-Suzuki conditions, i.e. Cp_2HfCl_2-AgOTf, (T. Matsumoto et al. (*Tetrahedron Lett*. 1988, *29*, 3567) in the presence of 2,6-di-t-butyl-4- methylpyridine leads, stereoselectively, to the β-glycoside **25** in

Scheme III[a]



The precise chemical mechanism accounting for the stereoselectivity of this glycoside bond formation is unknown but presumed to involve the participation of the neighboring group. Regioselective opening of the benzylidene ring by treatment with $NaCNBH_3$-HCl gives the

secondary alcohol **26** in 76% yield. Coupling of secondary alcohol **26** with fucosyl fluoride **7**, as disclosed by K.C. Nicolaou et al., (*J. Am. Chem. Soc.* **1990**, *112*, 3693), leads to the trisaccharide **27** with a yield of 95% with respect to the α-anomer. Trisaccharide **27** may be converted via a DAST-NBS reaction, as disclosed by K.C. Nicolaou et al. (*J. Am. Chem. Soc.* **1984**, *106*, 4189) to the glycosyl fluoride **28** in 80% yield. Fluoride **28** can serve as a common precursor to both sulfated Le^a **2** and the truncated version of sulfated Le^a **4**.

The synthesis of the tetrasaccharide **2** is achieved using a sequence involving the coupling of compound **28** with the galactose derivative **5** (Cp_2HfCl_2-AgOTf). This leads, stereoselectively, to compound **29** with a yield of 58%. The chloroacetate moiety can be removed from compound **29** and the sulfate group can be attached in its place ($SO_3 \cdot NMe_3$), furnishing compound **31** via compound **30** with an overall yield of 40%. The phthalimide and acetate groups are both removed from compound **31** by treatment with $NH_2NH_2 \cdot H_2O$ at 100°C. This may then be followed by acetylation of the generated amino group to give the amide **32** in 73% overall yield. Final deprotection to generate the naturally occurring compound **2** is then achieved by hydrogenolysis with a 95% yield.

Synthesis of the trisaccharide **4** may proceed by glycosylating benzyl alcohol with fluoride **28**. This leads to compound **33** with a yield of 95%. Compound **33** is then converted to trisaccharide **4** as described above for tetrasaccharide **2** (Scheme III).

The above syntheses render the natural sulfo-oligosaccharides **1** and **2**, as well as their simpler Le^x and Le^a sulfate analogs **3** and **4**. The products of these syntheses are yielded in pure form suitable for extensive biological investigations. Further studies

envisioned in this field may expand the library of biological tools and provide leads for therapeutic agents in the area of inflammation and related conditions.

Brief Description of the Drawings:

Fig.1 illustrates sulfated Lewis^x (1,3) and Lewis^a (2,4) target molecules and key intermediates (5 - 10) for their chemical synthesis.

Detailed Description:

General Techniques: All reaction were carried out under a dry argon atmosphere using freshly distilled solvents unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Benzene, methylene chloride and toluene were distilled from calcium hydride. All other anhydrous solvents were purchased from Aldrich Chemical Company Inc. Amine bases were dried and stored over potassium hydroxide. Glassware was either oven dried (120°C) or flame dried (0.05 torr) prior to use. Where necessary, compounds were dried by azeotropic removal of water with benzene or toluene under reduced pressure. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using uv light (254 nm) and/or heating with *p*-anisaldehyde solution (340 mL ethanol, 9.2 mL *p*-anisaldehyde, 12.5 mL sulfuric acid and 3.75 mL acetic acid). Reaction temperatures were measured externally unless otherwise noted. Solvents used for work-up, chromatography, and recrystallizations were reagent grade from either Fisher Scientific or E. Merck. Reactions were worked-up by washing with saturated aqueous solutions of the salts indicated. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040-0.063 mm). Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.

NMR spectra were recorded on Bruker AMX-500 MHz spectrometer at ambient temperature. Chemical shifts are reported relative to the residual solvent peak. Multiplicities are designated as singlet (s), doublet (d), triplet (t), pseudo triplet (PT), quartet (q), multiplet (m), broad (b), apparent (app) or obstructed (obs). IR samples were prepared by evaporation of a solution of the compound in $CHCl_3$ or $CDCl_3$ onto a NaCl plate under a stream of argon.1 IR spectra were recorded on a Perkin elmer 1600 series FT-IR spectrophotometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under Fast Atom Bombardment (FAB) conditions. Melting points were obtained with a Thomas Hoover Unimelt apparatus and are uncorrected. Microanalyses were performed at the Scripps ?Research Institute.

Abbreviations used herein are as follows: TES = $-SiEt_3$, TBS = $-Si^tBuMe_2$, THP = tetrahydropyranyl-, Ts = *p*-$MePhSO_2$, DMAP = p -(dimethylamino)pyridine, M.S. = molecular sieves, pyr = pyridine, MEM = methoxyethoxymethyl-, Ms = $-SO_2Me$, Tf = $-SO_2CF_3$, PMB = *p*-methoxybenzyl-, TMS = $-SiMe_3$.

Sulfated Le^x tetrasaccharide (compound 1): A method for synthesizing sulfated Le^x tetrasaccharide, i.e. compound 1, is illustrated in Scheme I (supra). The reaction conditions for each step of Scheme I are provided as follows:

Step "A": Compound 10 was combined with 2.0 equivalents of compound 5 with 3.0 equivalents of $AgClO_4$ and 3.0 equivalents of $SnCl_2$ with 4Å molecular sieves in CH_2Cl_2 and allowed to react for 4 hours starting at 0°C and increasing to 25°C to yield compound 11 with a 90% yield.

Step "B": Compound 11 was then combined with a

(1:1) mixture of hydrazine-EtOH at 95°C for 48 hours to produce compound **12**.

Step "C": Compound **12** was then combined with an excess of Ac_2O and with an excess of Et_3N, using *p*-(dimethylamino)pyridine (DMAP) as a catalyst, in CH_2Cl_2 at 25°C for 4 hours to produce compound **13** with an overall yield of 80% for the two steps.

Step "D": Compound **13** was then combined with 2.0 equivalents of Bu_4NF in THF at 25°C for 1 hour to produce compound **14** with a yield of 95%.

Step "E": Compound **14** was then combined with 2.0 equivalents of compound **6**, 3.0 equivalents of $AgClO_4$ and 3.0 equivalents of $SNCl_2$ with 4Å molecular sieves in CH_2Cl_2 and allowed to react for 5 hours starting at 0°C and increasing to 25°C to yield compound **15** with a 75% yield.

Step "F": Compound **15** was then combined with a catalytic amount of $H_2Ru(PPh_3)_4$ in EtOH at 95°C for 4 hours; the product was then combined with a catalytic amount of *p*-TsOH in MeOH at 25°C for 1 hour to produce compound **16** with a 81% yield.

Step "G": Compound **16** was then combined with 2.0 equivalents of compound **7**, 3.0 equivalents of $AgClO_4$ and 3.0 equivalents of $SNCl_2$ with 4Å molecular sieves in CH_2Cl_2 and allowed to react for 4 hours starting at 0°C and increasing to 25°C to yield compound **17** with a 85% yield.

Step "H": Compound **17** was then combined with 5.0 equivalents of thiourea, 2.0 equivalents of 2,6-lutidine in EtOH at 65°C for 5 hours to produce compound **18** with an 81% yield.

Step "I": Compound **18** was then combined with 20 equivalents of SO_3-NMe_3 in pyridine at 25°C for 24 hours to produce compound **19** with a 95% yield.

Step "J": Compound **19** was then combined with 2.0 equivalents of NaOMe in MeOH at 45°C for 5 hours; and then deprotected with H_2 using $Pd(OH)_2$ in a 2:1 mixture

of $MeOH-H_2O$ for 48 hours to produce compound **1** with a yield of 80%.

Truncated sulfated Le^x (trisaccharide 3): A method for synthesizing truncated sulfated Le^x, i.e., the trisaccharide **3**, is illustrated in Scheme II (supra). The reaction conditions for each step of Scheme II are provided as follows:

Step "A": Compound **5** was combined with 2.0 equivalents of compound **6** with 3.0 equivalents of $AgClO_4$ and 3.0 equivalents of $SnCl_2$ with 4Å molecular sieves in CH_2Cl_2 and allowed to react for 4 hours starting at 0°C and increasing to 25°C to yield compound **20** with a 81% yield.

Step "B": Compound **20** was then combined with a catalytic amount of $H_2Ru(PPh_3)_4$ in EtOH at 80°C for 1 hour; the product was then combined with a catalytic amount of *p*-TsOH in a 4:1 mixture of $MeOH-CH_2Cl_2$ at 25°C for 2 hours to produce compound **21** with a 82% yield.

Step "C": Compound **20** was combined with 2.0 equivalents of compound **7** with 3.0 equivalents of $AgClO_4$ and 3.0 equivalents of $SnCl_2$ with 4Å molecular sieves in a 3:1 mixture of Et_2O-THF and allowed to react for 3 hours starting at -15°C and increasing to 0°C to yield compound **22** with a 85% yield.

Step "D": Compound **22** was then combined with 5.0 equivalents of thiourea, 2.0 equivalents of 2,6-lutidine in a 1:1 mixture of $EtOH-CH_2Cl_2$ at 65°C for 5 hours to produce compound **23** with a 90% yield.

Step "E": Compound **23** was then combined with 20 equivalents of SO_3-NMe_3 in pyridine at 25°C for 24 hours to produce compound **24** with a 86% yield.

Step "F": Compound **24** was then combined with 2.0 equivalents of NaOMe in MeOH at 25°C for 4 hours; and then deprotected with H_2 using $Pd(OH)_2$ in MeOH for 7 days to produce compound **3** with a yield of 74%.

Sulfated Le^a (tetrasaccharide 2 and trisaccharide 4): A method for synthesizing sulfated Le^a tetrasaccharide 2 and the trisaccharide 4 is illustrated in Scheme III (supra). The reaction conditions for each step of Scheme III are provided as follows:

Step "A": Compound 8 was combined with 4.0 equivalents of compound 6, 5.0 equivalents of AgOTf (Tf=$-SO_2CF_3$), 5.0 equivalents of Cp_2HfCl_2, and 1.0 equivalent of 2,6-di-t-butyl-4-methylpyridine with 4Å molecular sieves in CH_2Cl_2 for 6 hours starting at 0°C and ending at 25°C to produce compound 25 with a yield of 63%.

Step "B": Compound 25 was then combined with 10.0 equivalents of $NaCNBH_3$ and excess ethereal HCl with 3Å molecular sieves in THF at 0°C for 30 minutes to produce compound 26 with a yield of 76%.

Step "C": Compound 26 was then combined with 2.0 equivalents of compound 7 with 4.0 equivalents of $AgClO_4$ and 4.0 equivalents of $SnCl_2$ with 4Å molecular sieves in a 5:1 mixture of Et_2O-THF and allowed to react for 1 hour starting at -15°C and increasing to 0°C to yield compound 27 with a 95% yield.

Step "D": Compound 27 was then combined with 3.0 equivalents of DAST and 1.25 equivalents of NBS in CH_2Cl_2 for 2 hour starting at -78°C and increasing to -20°C to yield compound 28 with a 80% yield.

Step "E": Compound 28 was then combined with 8.0 equivalents of benzyl alcohol, 5.0 equivalents of AgOTf (Tf=$-SO_2CF_3$), and 5 equivalents of Cp_2HfCl_2 with 4Å molecular sieves in CH_2Cl_2 for 18 hours starting at 0°C and ending at 25°C to produce compound 33 with a yield of 95%.

Step "F": Alternatively, compound 28 was then combined with 3.0 equivalents of compound 5, 3.0 equivalents of AgOTf (Tf=$-SO_2CF_3$), and 3.0 equivalents of Cp_2HfCl_2 with 4Å molecular sieves in CH_2Cl_2 for 4 hours starting at 0°C and ending at 25°C to produce

compound **29** with a yield of 58%.

Step "G": Compound **29** or **33** was then combined with 5.0 equivalents of thiourea, 2.5 equivalents of 2,6-lutidine in a 1:1 mixture of EtOH-CH_2Cl_2 at 65°C for 12 hours to produce compound **30** with a 79% yield or compound **34** with a yield of 89%, respectively.

Step "H": Compound **30** or **34** was then combined with 20 equivalents of SO_3-NMe_3 in pyridine at 25°C for 24 hours to produce compound **31** with a 50% yield or compound **35** with a 76% yield, respectively.

Step "I": Compound **31** or **35** was then first combined with a 1:1 mixture of hydrazine hydrate-EtOH at 100°C for 3 hours; the product was then combined with an excess of Ac_2O and with an excess of Et_3N in MEOH at 25°C for 10 minutes to produce compound **32** with an overall yield of 73% for the two steps or to produce compound **36** with an overall yield of 50%, respectively.

Step "J": Compound **32** or **36** was then deprotected with H_2 using $Pd(OH)_2$ in a 2:1 mixture of MeOH-H_2O for 48 hours at 25°C to produce compound **2** with a yield of 95% or compound **4** with a yield of 82%, respectively.

Intermediate compounds 8 and 10: A method for synthesizing intermediate compounds **8** and **10** is illustrated in Scheme IV (supra). The reaction conditions for each step of Scheme IV are provided as follows:

Step "A": Compound **37** was combined with 3.0 equivalents of benzaldehyde dimethyl acetal, with a catalytic amount CSA in THF for 16 hours at 55°C to produce compound **8** with a yield of 85%.

Step "B": Compound **8** was then combined with 2.0 equivalents of NaH, 2.0 equivalents of allyl bromide, and 0.1 equivalent of Bu_4NI in THF for 16 hours starting at 0°C and ending at 50°C to produce compound **38** with a yield of 91%.

Step "C": Alternatively, compound **37** was combined

with 10.0 equivalents of $NaCNBH_3$ and excess ethereal HCl with 3Å molecular sieves in THF for 1 hour starting at 0°C and ending at 25°C to produce compound **39**.

Step "D": Compound **39** was then combined with 1.5 equivalents of *t*-butyldimethylsilyl triflate (trifluoromethanesulphonate), 1.7 equivalents of 2,6-lutidine in CH_2Cl_2 for 1.5 hours starting at 0°C and ending at 25°C to produce compound **40** with a 75% yield for two steps.

Step "E": Alternatively, compound **39** was then combined with 3.0 equivalents of DAST and 1.2 equivalents of dimethyl(methylthio)sulfonium triflate (trifluoromethanesulphonate), i.e., DMTST, in CH_2Cl_2 for 1 hour at -10°C to produce compound **10** with a 50% yield.

Intermediate compound 5: A method for synthesizing intermediate compound 5 is illustrated in Scheme V (supra). The reaction conditions for each step of Scheme V are provided as follows:

Step "A": Compound **41** was combined with excess 2,2-dimethoxypropane and a catalytic amount CSA in acetone for 48 hours at 25°C to produce compound **42** with a yield of 56%.

Step "B": Compound **42** was then combined with 3.0 equivalents of NaH, 3.0 equivalents of benzyl bromide, and a catalytic amount Bu_4NI in THF for 2 hours starting at 0°C and ending at 50°C to produce compound **43** with a yield of 89%.

Step "C": Compound **43** was then combined with 3.0 equivalents of DAST and 1.2 equivalents of NBS in CH_2Cl_2 for 4 hour starting at -5°C and increasing to 10°C to yield compound **44** with a 80% yield.

Step "D": Alternatively, compound **41** was then combined with 3.0 equivalents of benzyl alcohol, 3.0 equivalents of $AgClO_4$, and 1.5 equivalents of Cp_2ZrCl_2 with 4Å molecular sieves in benzene for 2 hours to

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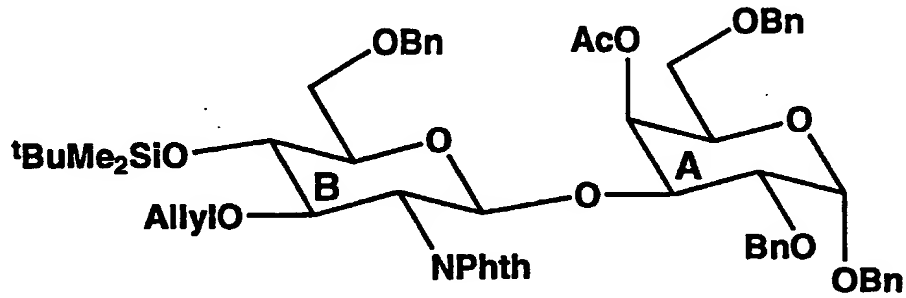
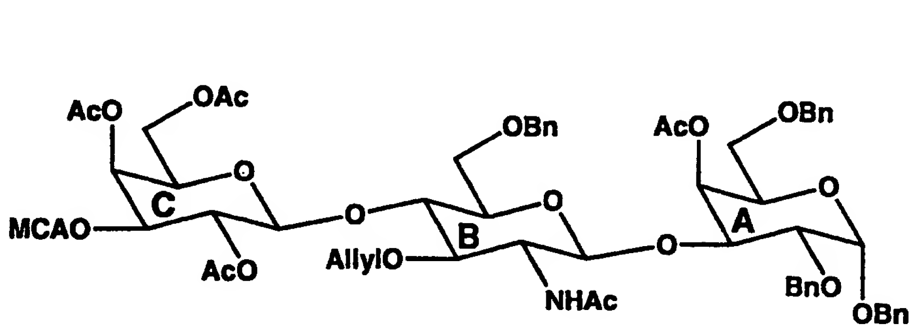
combined with an excess of HF-pyridine and 1.3 equivalents of NBS in CH_2Cl_2 for 6 hour starting at -78°C and increasing to 0°C to yield compound 6 with a 76% yield.

The chemical intermediates were physically characterized as follows:



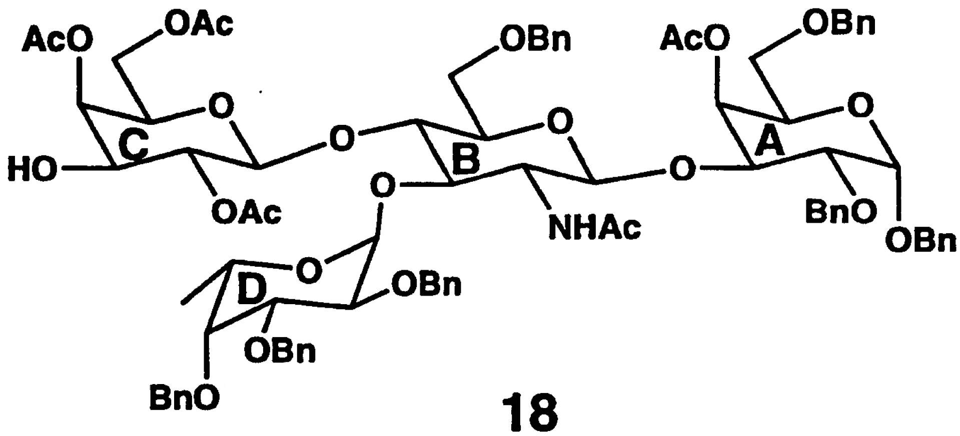
11

11: R_f = 0.45 (silica, 95:5, dichloromethane:ether); $[\alpha]_D^{25}$ +62.2 ° (c = 0.785, chloroform): IR (film) ν_{max} 3029 (w), 2928 (m), 2959 (m), 1775 (w), 1746 (m), 1715 (s), 1457 (m), 1386 (s), 1223 (s), 1106 (s), 1061 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) ∂ 7.81-7.60 (m, 4 H, aromatic), 7.37-7.07 (m, 18 H, aromatic), 6.83-6.81 (m, 2 H, aromatic), 5.55-5.47 (m, 2 H, H-4A, CH=CH_2), 5.36 (d, J = 7.8 Hz, 1 H, H-1B), 4.89 (m, 1 H, -CH=CH_2), 4.71 (m, 1 H, -CH=CH_2), 4.66-4.58 (m, 3 H, OCH_2Ph), 4.55 (d, J = 3.8 Hz, 1 H, H-1A), 4.48-4.36 (m, 3 H, OCH_2Ph), 4.18-4.08 (m, 5 H, C*H*O), 4.02 (dd, J = 4.3, 7.0 Hz, 1 H, C*H*O), 3.85 (d, J = 12.7 Hz, 1 H, OCH_2-CH=CH_2), 3.78-3.54 (m, 5H, C*H*O), 3.49 (dd, J = 3.8, 10.0 Hz, 1 H, H-2A), 3.43 (dd, J = 3.7, 10.1 Hz, 1 H, H-3A), 3.34 (dd, J = 7.2, 10.2 Hz, 1 H, C*H*O), 2.04 (s, 3 H, acetate), 0.85 (s, 9 H, -SiC(CH_3)$_3$), 0.07, 0.04 (s, 3 H each, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 170.2, 138.8, 138.2, 138.0, 136.7, 134.4, 133.9, 131.7, 128.5, 128.3, 128.25, 128.20, 128.1, 128.0, 127.8, 127.52, 127.49, 127.34, 127.28, 127.24, 127.20, 127.0, 123.2, 116.4, 99.0, 95.5, 79.7, 76.2, 75.5, 75.1, 73.6, 73.3, 73.2, 72.8, 71.8, 71.5, 69.4, 69.1, 68.8, 68.3, 56.5, 25.9, 20.8, 17.9, -4.0, -4.6; HRMS (LSIMS) Calcd for $C_{59}H_{69}NO_{13}SiCs$ (M+Cs): 1160.3593, found: 1160.3586.



15

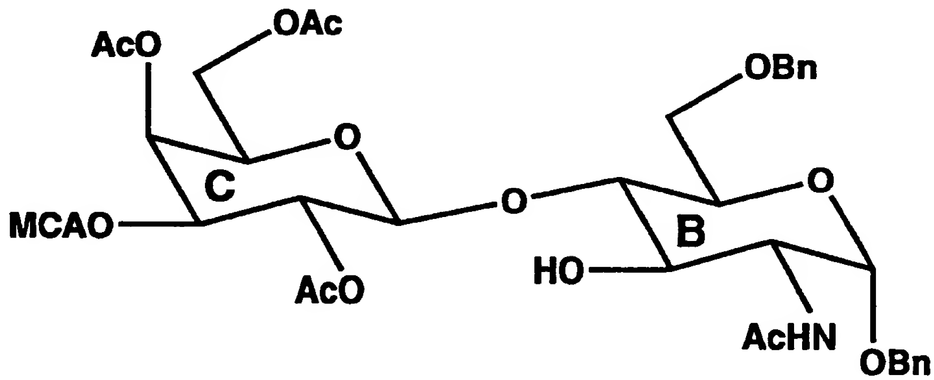
15: R_f = 0.20 (silica, 1:1, ethyl acetate:petroleum ether); $[\alpha]_D^{25}$ +24.5 o (c = 2.2, chloroform): IR (film) ν_{max} 3389 (w), 2924 (m), 2870 (w), 1748 (s), 1667 (m), 1538 (w), 1371 (s), 1228 (s), 1056 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 20 H, aromatic), 5.84 (m, 1 H, -C*H*=CH_2), 5.64 (d, *J* = 9.0 Hz, 1 H, NH), 5.45 (d, *J*, 3.0 Hz, 1 H, H-4A), 5.31 (d, *J* = 3.2 Hz, 1 H, H-4C), 5.23 (m, 1 H, -CH=CH_2), 5.16-5.08 (m, 2 H, -H-2C, -CH=CH_2), 4.95 (dd, *J* = 3.3, 10.5 Hz, 1 H, H-3C), 4.86-4.83 (m, 2 H, OCH_2Ph), 4.70-4.63 (m, 3 H, OCH_2Ph), 4.55-4.44 (m, 6 H, C*H*O), 4.19-4.05 (m, 6 H, C*H*O), 3.99-3.94 (m, 3 H, CH_2Cl, C*H*O), 3.87-3.65 (m, 5 H, C*H*O), 3.62 (t, *J* = 6.6 Hz, 1 H, C*H*O), 3.52-3.39 (m, 3 H, C*H*O), 2.13, 2.06, 2.03, 1.99, 1.80 (s, 3 H each, acetyls); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 170.4, 170.2, 170.1, 169.84, 169.76, 166.5, 138.3, 138.2, 137.9, 136.9, 135.0, 128.7, 128.52, 128.49, 128.43, 128.40, 128.35, 128.29, 128.26, 128.20, 127.07, 127.95, 127.90, 127.84, 127.77, 127.72, 127.69, 127.64, 127.60, 127.56, 127.38, 127.29, 116.3, 101.0, 99.6, 95.6, 78.3, 76.1, 75.0, 74.9, 74.2, 73.6, 73.3, 72.8, 72.4, 71.6, 70.9, 70.4, 69.2, 69.1, 68.8, 68.5, 66.6, 60.8, 53.0, 40.4, 29.6, 23.2, 20.9, 20.7, 20.6; HRMS (LSIMS) Calcd for $C_{61}H_{72}NO_{21}ClCs$ (M+Cs): 1322.3340, found: 1322.3301.



18

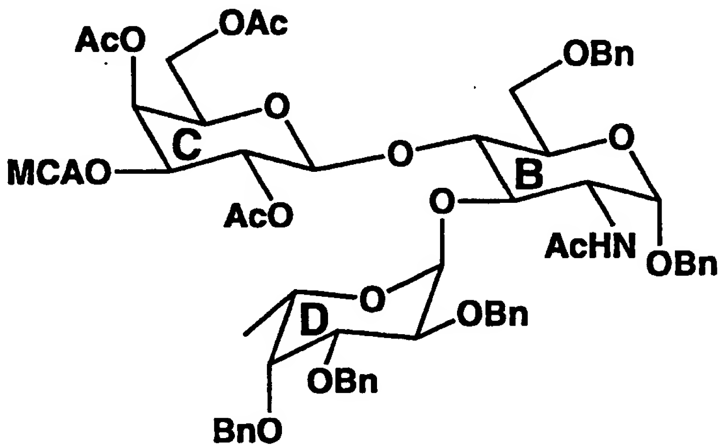
18: R_f = 0.20 (silica, 1:1, ether:dichloromethane); $[\alpha]_D^{25}$ +4.4 ° (c = 1.00, chloroform): IR (film) ν_{max} 3377 (s), 2922 (m), 2866 (m), 1742 (s), 1661 (m), 1365 (m), 1230 (s), 1096 (s), 1049 (s), 739 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.19 (m, 35 H, aromatic), 5.70 (d, *J* = 8.2 Hz, 1 H, NH), 5.48 (d, *J* = 2.9 Hz, 1 H, H-4A), 5.21 (d, *J* = 3.3 Hz, 1 H, H-4C), 5.19 (d, *J* = 3.6 Hz, 1 H, H-1D), 5.03 (d, *J* = 6.2 Hz, 1 H, H-1B), 4.49 (d, *J* = 11.8 Hz, 1 H, OCH_2Ph), 4.87-4.63 (m, 9 H, C*H*O), 4.58-4.42 (m, 7 H, C*H*O), 4.37 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.17-3.97 (m, 7 H, C*H*O), 3.89 (dd, *J* = 2.2, 10.1 Hz, 1 H, C*H*O), 3.81-3.53 (m, 7 H, C*H*O), 3.47-3.37 (m, 3 H, C*H*O), 2.62 (bs, 1 H, O*H*), 2.04, 2.02, 1.99, 1.91, 1.64 (s, 3 H each, acetyls), 1.13 (d, *J* = 6.4 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.6, 170.4, 170.1, 169.7, 138.9, 138.7, 138.5, 138.3, 138.1, 137.9, 136.9, 128.7, 128.60, 128.56, 128.48, 128.45, 128.42, 128.38, 128.34, 128.29, 128.24, 128.20, 128.16, 128.10, 128.06, 128.04, 127.96, 127.90, 127.86, 127.82, 127.76, 127.73, 127.65, 127.58, 127.53, 127.47, 127.20, 127.16, 127.03 126.93, 100.2, 99.1, 96.7, 95.7, 79.6, 76.0, 75.9, 75.4, 74.6, 74.5, 74.2, 73.8, 73.7, 73.4, 73.1, 72.9, 72.8, 72.6, 72.4, 71.0, 70.7, 70.4, 69.2, 69.0, 68.4, 68.0, 66.1, 60.6, 29.6, 23.1, 20.8, 20.7, 20.64, 20.61, 16.7; HRMS (LSIMS)

Calcd for $C_{83}H_{95}NO_{24}Cs$ (M+Cs): 1622.5298, found: 1622.5304.



21

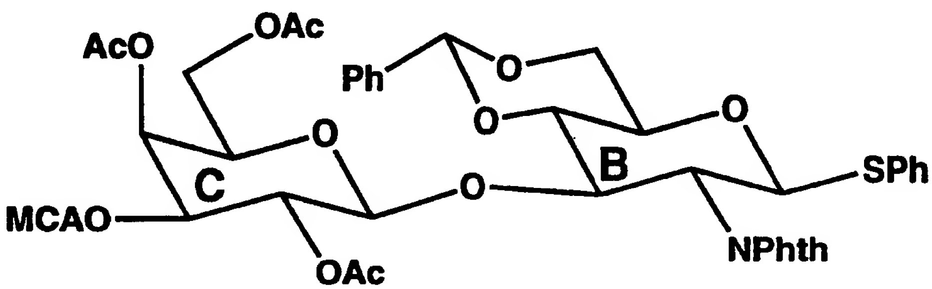
21: R_f = 0.25 (silica, 4:1, dichloromethane:acetone); $[\alpha]_D^{25}$ +75.9 ° (c = 1.00, chloroform): IR (film) ν_{max} 3487 (s), 2927 (s), 1750 (s), 1665 (m), 1536 (m), 1372 (s), 1223 (s), 1047 (s), 748 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.27 (m, 10 H, aromatic), 5.65 (bd, 1 H, NH), 5.33 (d, J = 3.3 Hz, 1 H, H-4C), 5.19 (dd, J = 8.1, 10.4 Hz, 1 H, H-2C), 4.97 (d, J = 2.6 Hz, 1 H, H-1B), 4.93 (dd, J = 3.4, 10.4 Hz, 1 H, H-3C), 4.77 (d, J = 12.1 Hz, 1 H, OCH_2Ph), 4.69 (d, J = 11.8 Hz, 1 H, OCH_2Ph), 4.49-4.44 (m, 2 H, OCH_2Ph), 4.40 (d, J = 8.1 Hz, 1 H, H-1C), 4.20-4.16 (m, 1 H, CHO), 4.11 (d, J = 6.5 Hz, 2 H, H-6C), 3.95 (s, 2 H, CH_2Cl), 3.88 (bt, J = 6.5 Hz, 1 H, H-5C), 3.82-3.71 (m, 3 H, CHO), 3.66 (dd, J = 2.5, 10.8 Hz, 1 H, H-6B), 3.58 (d, J = 10.8 Hz, 1 H, H-6B), 2.14, 2.06, 1.98, 1.97 (s, 3 H each, acetyls); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.1, 166.5, 137.9, 137.0, 128.54, 128.50, 128.05, 127.97, 127.89, 127.87, 127.82, 101.0, 96.8, 81.1, 73.6, 72.4, 70.9, 70.3, 69.9, 69.7, 68.3, 67.5, 66.6, 61.1, 52.8, 40.2, 23.3, 20.7, 20.6, 20.5; HRMS (LSIMS) Calcd for $C_{36}H_{44}NO_{15}ClCs$ (M+Cs); 898.1454, found 898.1456.



22

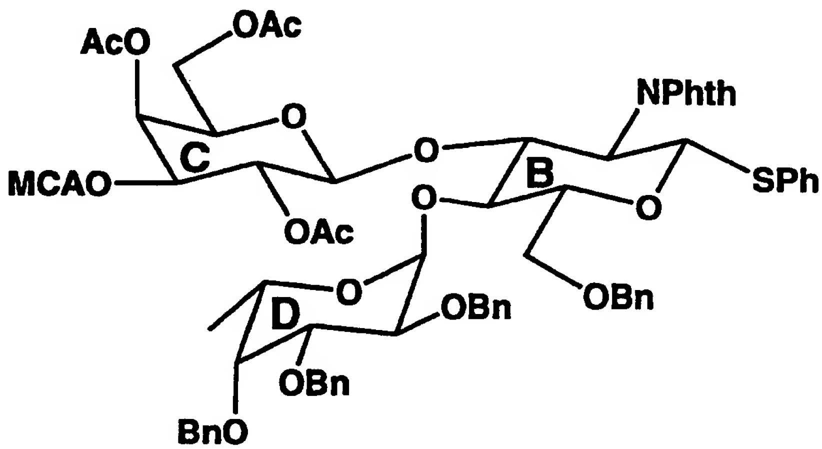
22: R_f = 0.70 (silica, 1:1, ether:dichloromethane); $[\alpha]_D^{25}$ +7.2 ° (c = 1.07, chloroform): IR (film) ν_{max} 3031 (s), 2932 (m), 1752 (s), 1628 (m), 1551 (w), 1370 (m), 1221 (s), 1048 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.12 (m, 25 H, aromatic), 6.65 (d, *J* = 7.3 Hz, 1 H, NH), 5.23 (d, *J* = 3.4 Hz, 1 H, H-1D), 5.20 (d, *J* = 3.3 Hz, 1 H, H-4C), 5.08 (d, *J* = 3.6 Hz, 1H, H-1B), 5.01 (dd, *J* = 8.1, 10.3 Hz, 1 H, H-2C), 4.95 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.80 (d, *J* = 12.1 Hz, 1 H, OCH_2Ph), 4.78-4.72 (m, 3 H, CHO), 4.71-4.63 (m, 4 H, OCH_2Ph), 4.54 (d, *J* = 8.1 Hz, 1 H, H-1C), 4.50 (d, *J* = 12.1 Hz, 1 H, OCH_2Ph), 4.41 (d, *J* = 12.1 Hz, 1 H, OCH_2Ph), 4.27 (bq, *J* = 6.5 Hz, 1 H, H-5D), 4.15-4.08 (m, 3 H, CHO), 4.03-3.97 (m, 3H, CHO), 3.94-3.91 (m, 3 H, CH_2Cl, CHO), 3.77 (dd, *J* = 2.8, 11.1 Hz, 1 H, H-6B), 3.70 (d, *J* = 1.7 Hz, 1 H, H-4D), 3.63-3.60 (m, 1 H, H-5B), 3.55 (dd, *J* = 1.6, 11.1 Hz, 1 H, H-6B), 3.45 (bt, *J* = 7.3 Hz, 1 H, CHO), 1.99, 1.97, 1.96, 1.55 (s, 3 H each, acetyls), 1.22 (d, *J* = 6.5 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 168.9, 166.5, 138.55, 138.52, 137.7, 137.5, 137.4, 128.7, 128.62, 128.58, 128.55, 128.45, 128.41, 128.32, 128.30, 128.26, 128.23, 128.20, 128.16, 128.07, 128.04, 127.98,

127.94, 127.86, 127.82, 127.67, 127.55, 127.43, 127.40, 127.37, 127.28, 127.03, 99.2, 98.8, 96.3, 79.7, 77.5, 77.2, 77.1, 75.3, 75.0, 746., 74.2, 73.6, 72.8, 72.6, 70.9, 70.4, 70.0, 69.1, 67.6, 66.6, 60.5, 53.8, 40.4, 22.7, 20.8, 20.6, 20.5, 16.8; HRMS (LSIMS) Calcd for $C_{63}H_{72}NO_{19}ClCs$ (M+Cs): 1314.3441, found: 1314.3451.



25

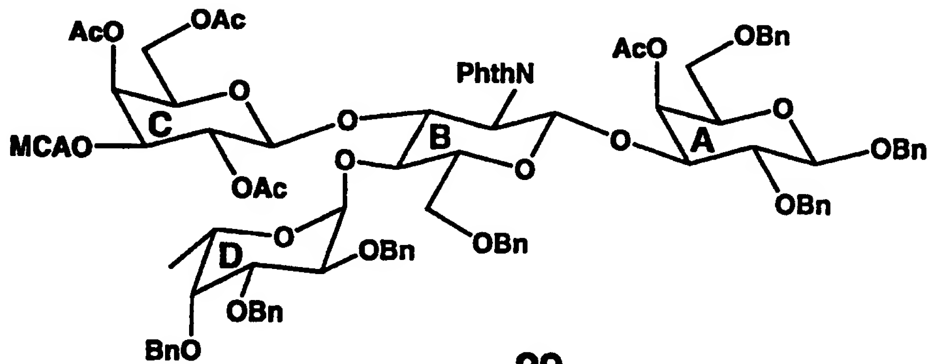
25: R_f = 0.35 (silica, 95:5, dichloromethane:ether); $[\alpha]_D^{25}$ +24.0 ° (c = 1.00, chloroform): IR (film) ν_{max} 3349 (br), 3026 (m), 2962 (m), 1749 (s), 1715 (s), 1377 (m), 1221 (s), 1101 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.77 (m, 4 H, aromatic), 7.49-7.23 (m, 10 H, aromatic), 5.58 (s, 1 H, C*H*Ph), 5.57 (d, *J* = 6.7 Hz, 1 H, H-1B), 5.18 (d, *J* = 3.4 Hz, 1 H, H-4C), 5.01 (dd, *J* = 8.0, 10.4 Hz, 1 H, H-2C), 4.80 (dd, *J* = 3.4, 10.4 Hz, 1 H, H-3C), 4.75 (dd, *J* = 8.9, 9.7 Hz, 1 H, C*H*O), 4.55 (d, *J* = 8.0 Hz, 1 H, H-1C), 4.43-4.38 (m, 2 H, C*H*O), 4.03 (dd, *J* = 8.3, 11.1 Hz, 1 H, H-6C), 3.88-3.79 (m, 5 H, CH_2Cl, C*H*O), 3.75-3.72 (m, 1 H, C*H*O), 3.48 (m, 1 H, C*H*O), 2.08, 1.92, 1.53 (s, 3 H each, acetates); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.9, 168.7, 166.5, 136.9, 132.75, 132.72, 131.3, 129.3, 129.0, 128.9, 128.41, 128.38, 128.35, 128.2, 126.02, 125.99, 125.94, 101.5, 100.2, 91.9, 84.2, 80.7, 76.6, 72.7, 72.5, 71.5, 70.5, 70.1, 68.8, 68.5, 67.4, 66.5, 66.3, 60.8, 60.5, 54.2, 40.2, 20.6, 20.5, 20.0; HRMS (LSIMS) Calcd for $C_{41}H_{40}NO_{15}ClSCs$ (M+Cs): 986.0862, found: 986.0868.



27

27: R_f = 0.40 (silica, 36:65, ethyl acetate:petroleum ether); $[\alpha]_D^{25}$ -8.7 ° (c = 2.40, chloroform): IR (film) ν_{max} 3027 (m), 2930 (m), 2873 (m), 1752 (s), 1715 (s), 1607 (w), 1452 (m), 1376 (s), 1219 (s), 1076 (s), 740 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.80 (m, 4 H, aromatic), 7.45-7.11 (m, 25 H, aromatic), 5.32 (d, J = 10.4 Hz, 1 H, H-1 B), 5.18 (d, J = 3.4 Hz, 1 H, H-4C), 5.17 (d, J = 3.9 Hz, 1 H, H-1D), 5.02 (dd, J = 8.2, 10.4 Hz, 1 H, H-2C), 4.98 (d, J = 12.3 Hz, 1 H, OCH_2Ph), 4.90 (d, J = 11.6 Hz, 1 H, OCH_2Ph), 4.85-4.68 (m, 7 H, C*H*O), 4.46 (dd, J = 3.4, 10.4 Hz, 1 H, H-3C), 4.40 (s, 2 H, OCH_2Ph), 4.35 (t, J = 10.3 Hz, 1 H, C*H*O), 4.25-4.17 (m, 3 H, C*H*O), 4.02-3.94 (m, 4 H, C*H*O), 3.81 (s, 2 H, CH_2Cl), 3.75 (bs, 1 H, H-4D), 3.70-3.62 (m, 2 H, C*H*O), 2.00, 1.98, 1.70 (s, 3 H each, acetates), 1.28 (d, J = 6.5 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.8, 169.2, 166.5, 138.6, 138.2, 138.15, 132.5, 131.6, 128.75, 128.70, 128.6, 128.43, 128.40, 128.36, 128.30, 128.25, 128.22, 128.17, 128.14, 128.11, 127.93, 127.75, 127.59, 127.52, 127.49, 127.46, 127.42, 127.36, 127.29, 127.26, 126.9, 123.7, 100.4, 97.7, 91.8, 83.3, 80.8, 79.9, 79.0, 77.2, 76.4, 76.0, 75.8, 75.4, 74.8, 74.7, 73.7, 73.4, 73.0, 72.9, 72.7, 72.6, 72.1, 70.0,

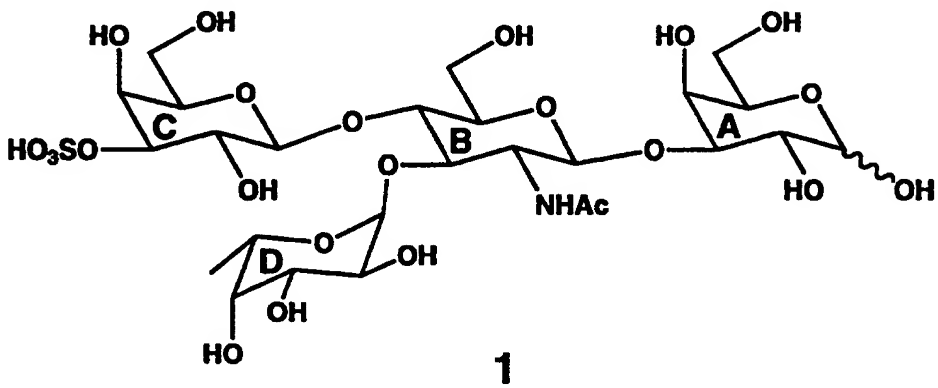
67.3, 66.6, 66.2, 66.0, 59.5, 55.2, 40.2, 20.5, 20.4, 16.9, 16.7; HRMS (LSIMS) Calcd for $C_{68}H_{70}NO_{19}SClCs$ (M+Cs): 1404.3006, found: 1404.2911.



29

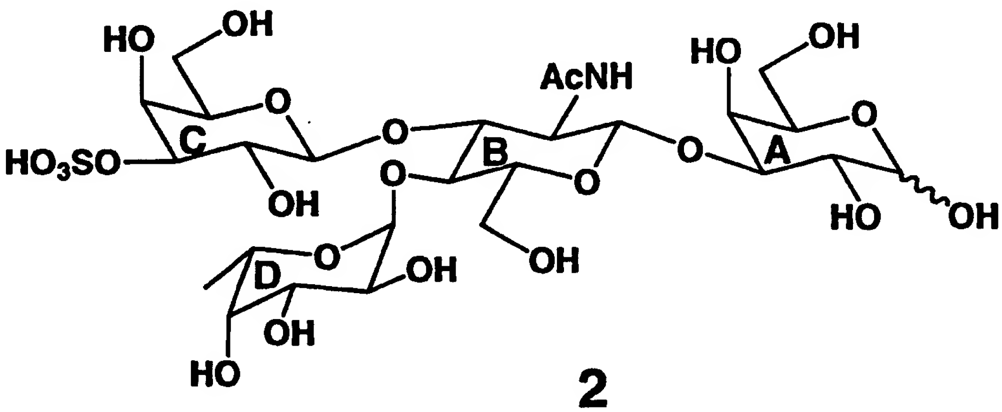
29: R_f = 0.33 (silica, 93:7, dichloromethane:ether); $[\alpha]_D^{25}$ -7.9 ° (c = 1.00, chloroform): IR (film) ν_{max} 3029 (w), 2930 (m), 2872 (m), 1751 (s), 1716 (s), 1454 (m), 1375 (s), 1222 (s), 1072 (s), 741 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-6.90 (m, 39 H, aromatic), 5.30 (d, J = 3.7 Hz, 1H, H-4A), 5.13 (d, J = 3.9 Hz, 1 H, H-1D), 5.10 (m, 2 H, H-1B, H-4C), 4.92 (dd, J = 8.1, 10.4 Hz, 1 H, H-2C), 4.90 (d, J = 12.2 Hz, 1 H, OCH_2Ph), 4.82-4.63 (m, 8 H, C*H*O), 4.48-4.34 (m, 8 H, C*H*O), 4.24 (d, J = 7.8 Hz, 1 H, H-1A), 4.18-4.07 (m, 3 H, C*H*O), 3.97-3.91 (m, 2 H, C*H*O), 3.87 (d, J = 10.7 Hz, 2 H, H-6A), 3.73 (s, 2 H, CH_2Cl), 3.67-3.42 (m, 9 H, C*H*O), 3.28 (dd, J = 7.8, 9.5 Hz, 1 H, H-2B), 1.97, 1.91, 1.88, 1.62 (s, 3 H each, acetates), 1.19 (d, J = 6.6 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 170.0, 169.8, 169.1, 166.6, 138.7, 138.6, 138.5, 138.21, 138.17, 137.8, 136.7, 134.4, 128.7, 128.41, 128.38, 128.36, 128.32, 128.28, 128.22, 128.19, 128.14, 128.08, 128.04, 128.00, 127.85, 127.75, 127.72, 127.67, 127.58, 127.54, 127.4, 127.3, 127.2, 127.1, 126.9, 126.8, 123.3, 102.2, 100.2, 98.4, 97.5, 80.8, 78.4, 77.2, 76.1, 75.6, 75.3, 74.8, 74.2, 73.8, 73.6, 72.9, 72.8, 72.7, 72.5, 72.1, 71.0, 70.0, 69.9, 69.0, 67.4, 67.1, 66.1, 66.0, 59.5, 56.6, 40.2, 20.7, 20.5,

20.4, 20.3, 16.9; HRMS (LSIMS) Calcd for $^{13}C_1C_{90}H_{96}NO_{26}ClCs$ (M+Cs): 1786.4963, found: 1786.5099.



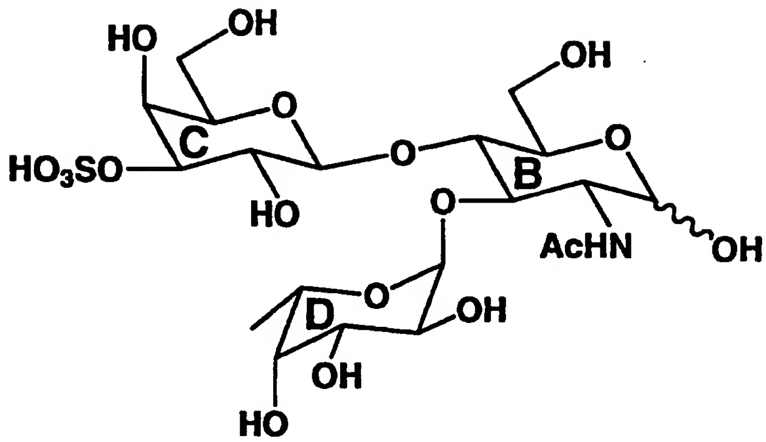
1

1: R_f = 0.45 (silica, 40:55:5, chloroform:methanol:water); $[\alpha]_D^{25}$ -39.1 ° (c = 0.85, methanol): IR (KBr) ν_{max} 3396 (br), 1653 (s), 1221 (m), 1089 (s), 762 (m), 619 (m) cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.16 (d, J = 3.7 Hz, 0.5 H, H-1Aα), 5.07 (d, J = 3.9 Hz, 1 H, H-1D), 4.66 (d, J = 8.5 Hz, 0.5 H, H-1Aß), 4.52 (d, J = 8.4 Hz, 1 H, H-1C), 4.50 (d, J = 8.4 Hz, 1 H, H-1B), 4.26 (dd, J = 3.2, 9.9 Hz, 1 H, H-3C), 4.21 (d, J = 3.2 Hz, 1 H, H-4C), 4.15 (d, J = 3.1 Hz, 0.5 H, H-4Aß), 4.10 (d, J = 3.3 Hz, 0.5 H, H-4Aα), 4.05-3.53 (m, 17 H, C*H*O), 3.46 (dd, J = 8.3, 9.9 Hz, 1 H, H-2B), 1.97 (s, 3 H, acetyl), 1.12 (d, J = 6.6 Hz, 3 H, H-6D), ^{13}C NMR (125 MHz, CD_3OD) δ 168.9, 103.7, 100.1, 93.9, 82.1, 76.2, 76.1, 74.5, 73.5, 72.7, 71.0, 69.7, 68.2, 67.8, 62.7, 62.4, 57.5, 23.2, 16.5; MS (LSIMS): 770 (M-H).



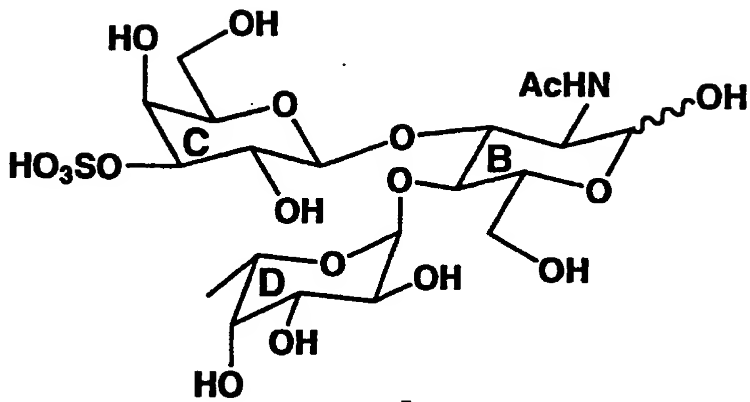
2

2: R_f = 0.21 (silica, 2:2:1, ethyl acetate:2-propanol:water); $[\alpha]_D^{25}$ -30.9 ° (c = 0.75, methanol): IR (film) v_{max} 3382 (br), 2928 (w), 1639 (m), 1232 (m), 1069 (s), 813 (m), 709 (w) cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.19 (d, *J* = 3.8 Hz, 0.5 H, H-1Aα), 5.00 (d, *J* = 3.8 Hz, 1 H, H-1D), 4.83 (bq, *J* = 6.5 Hz, 1 H, H-5D), 4.69 (d, *J* = 8.4 Hz, 0.5 H, H-1Aß), 4.58 (d, *J* = 7.7 Hz, 1 H, H-1C), 4.53 (d, *J* = 7.9 Hz, 1 H, H-1B), 4.29-4.24 (m, 2 H, H-3C, H-4C), 4.18-4.05 (m, 2 H, C*H*O), 3.94-3.49 (m, 17 H, C*H*O), 2.02 (s, 3 H, acetyl), 1.15 (d, *J* = 6.5 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, CD_2OD) δ 71.2 104.5, 103.8, 99.6, 98.8, 94.3, 84.1, 82.1, 80.7, 78.0, 77.2, 76.2, 73.7, 73.4, 72.8, 71.2, 70.6, 70.0, 69.9, 69.4, 68.0, 67.7, 62.7, 62.6, 62.5, 61.1, 57.5, 23.3, 16.6; HRMS (LSIMS) Calcd for $C_{26}H_{44}NO_{23}SCs_2$ (M-H+2Cs): 1036.0134, found 1036.0134.



3

3 : R_f = 0.15 (silica, 60:35:5, chloroform:methanol:water); $[\alpha]_D^{25}$ -23.2 ° (c = 0.60, methanol): IR (film) ν_{max} 3367 (br), 2937 (m), 1642 (s), 1549 (m), 1425 (w), 1378 (m), 1241 (s), 1072 (s), 816 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.02 (m, 1 H, H-1D), 4.96 (d, J = 3.3 Hz, 0.5 H, H-1Bα), 4.86 (bq, J = 6.6 Hz, 1 H, H-5D), 4.61 (d, J = 8.0 Hz, 0.5 H, H-1Bß), 4.55 (m, 1 H H-1C), 4.23-4.14 (m, 3 H, C*H*O), 4.05-4.00 (m, 2 H, C*H*O), 3.97-3.83 (m, 4 H, C*H*O), 3.80-3.58 (m, 6 H, C*H*O), 3.50 (bt, J = 6.0 Hz, 1 H, C*H*O), 1.97 (s, 3 H, acetyl), 1.16 (m, 3 H, H-6D); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 103.7, 100.4, 93.0, 82.3, 77.4, 76.3, 76.2, 75.5, 75.1, 74.4, 73.7, 72.8, 71.2, 71.1, 70.0, 69.9, 68.2, 67.6, 62.7, 61.3, 55.8, 22.8, 16.6; HRMS (LSIMS) Calcd for $C_{20}H_{35}NO_{18}S$ (M+):609.1575, found 609.1598.

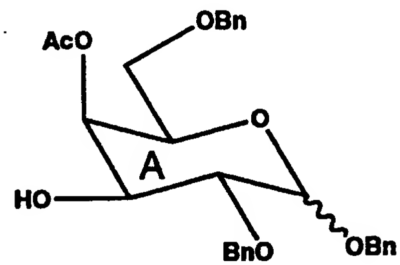


4

4 : R_f = 0.14 (silica, 60:35:5, chloroform:methanol:water); $[\alpha]_D^{25}$ -43.3 ° (c = 0.42, methanol): IR (film) ν_{max} 3450 (br), 2921 (w), 1639 (m), 1224 (m), 1072 (s), 1033 (s) cm^{-1}, ^1H NMR (500 MHz, CD_3OD) δ 5.08 (bs, 0.5 H, H-1Bα), 4.99 (bs, 1 H, H-1D), 4.68 (d, J = 8.6 Hz, 0.5 H, H-1Bß), 4.56 (m, 1 H, H-1C), 4.30-3.50 (m, 16 H, C*H*O), 2.01 (s, 3 H, acetyl), 1.15 (d, J = 6.2 Hz, 3 H, H-6D); ^{13}C NMR (125 MHz, CD_3OD) δ 172.4, 104.7, 99.6, 96.7, 92.9, 82.4, 76.3, 76.1, 74.0, 73.7, 72.9, 71.2, 70.5, 70.1, 68.1, 67.6, 62.8, 61.5, 58.9, 55.7, 22.9, 16.6; HRMS (LSIMS) calcd for $C_{20}H_{34}NO_{18}SCs_2$ (M-H+2Cs): 873.9605, found 873.9601.

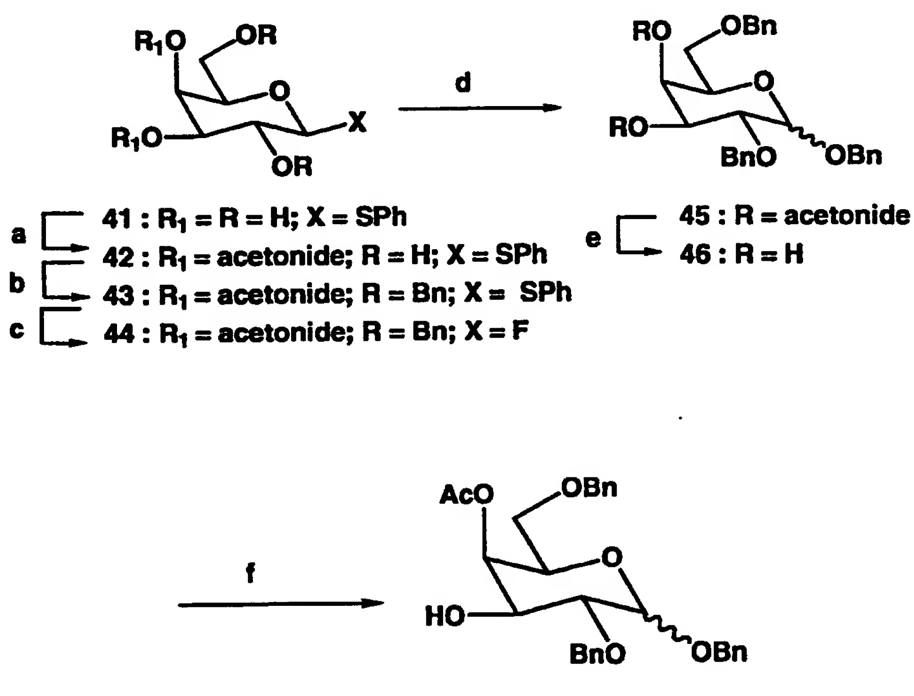
What is claimed is:

1. Compound 5 having the following structure:



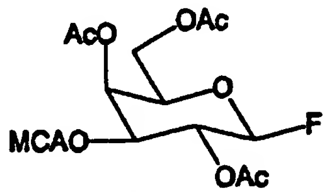
5

2. A method for making compound 5 comprising the following steps:



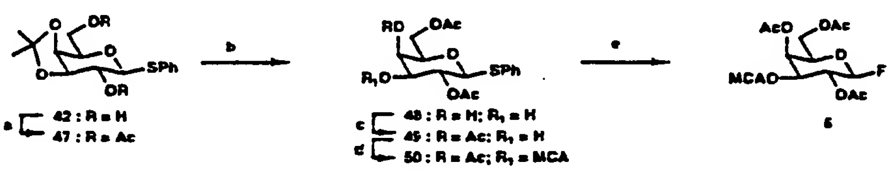
5

3. Compound 6 having the following structure:

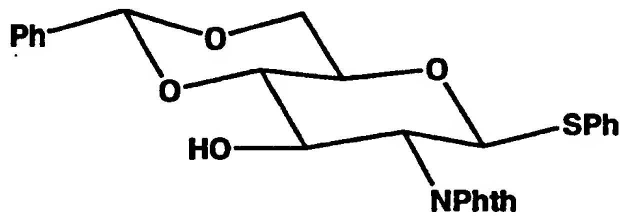


6

4. A method for making compound 6 comprising the following steps:

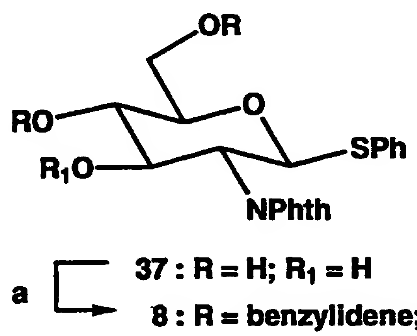


5. Compound **8** having the following structure:



8

6. A method for making compound **8** comprising the following steps:

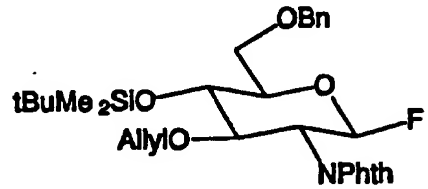


a

37 : R = H; R_1 = H

8 : R = benzylidene; R_1 = H

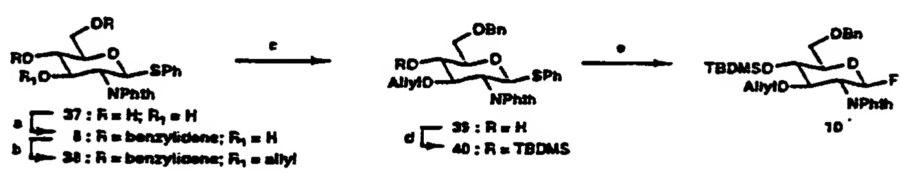
7. Compound 10 having the following structure:



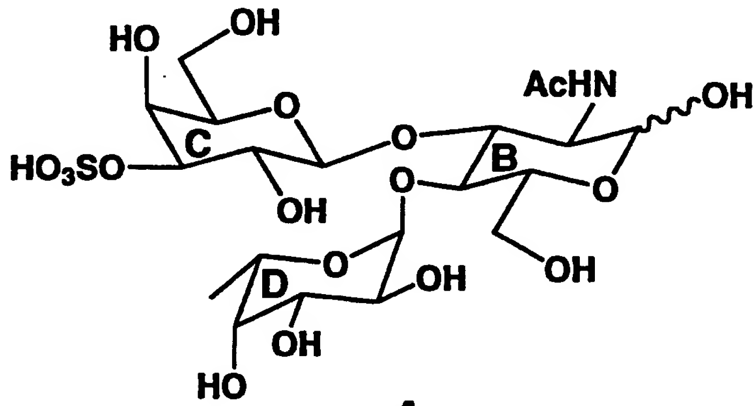
[from D-glucosamine]

10

8. A method for making compound 10 comprising the following steps:

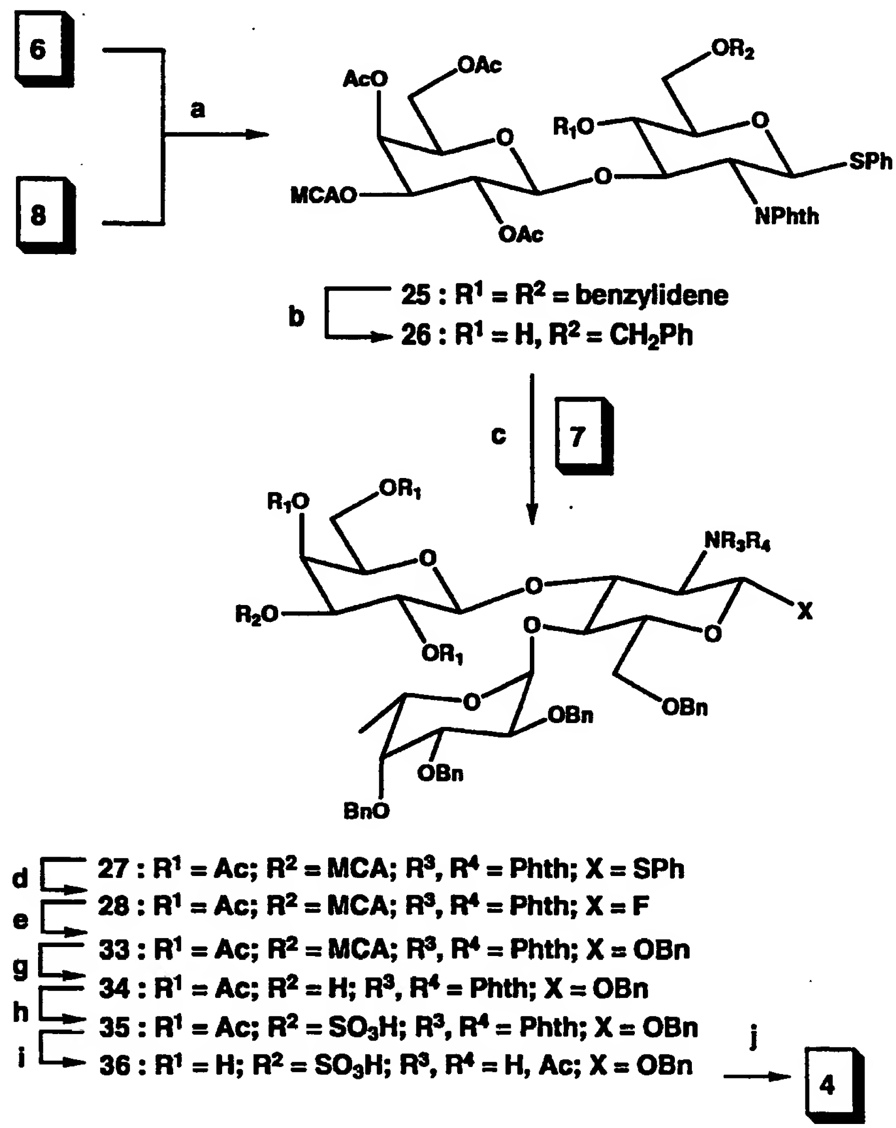


9. Compound 4 having the following structure:

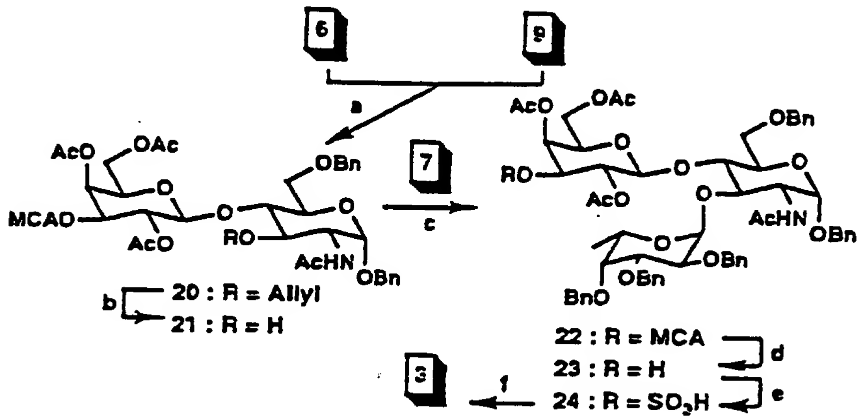


4

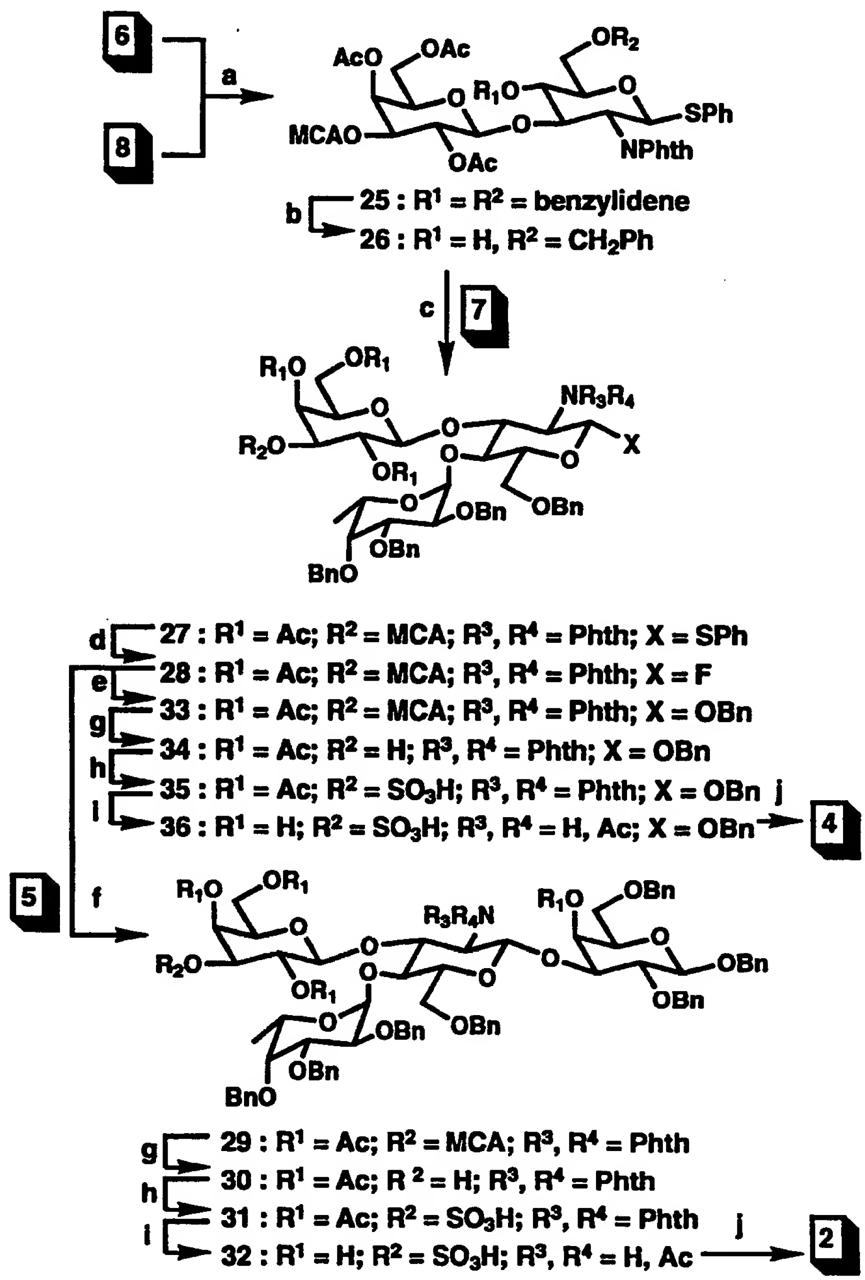
10. A method for making compound 4 comprising the following steps:



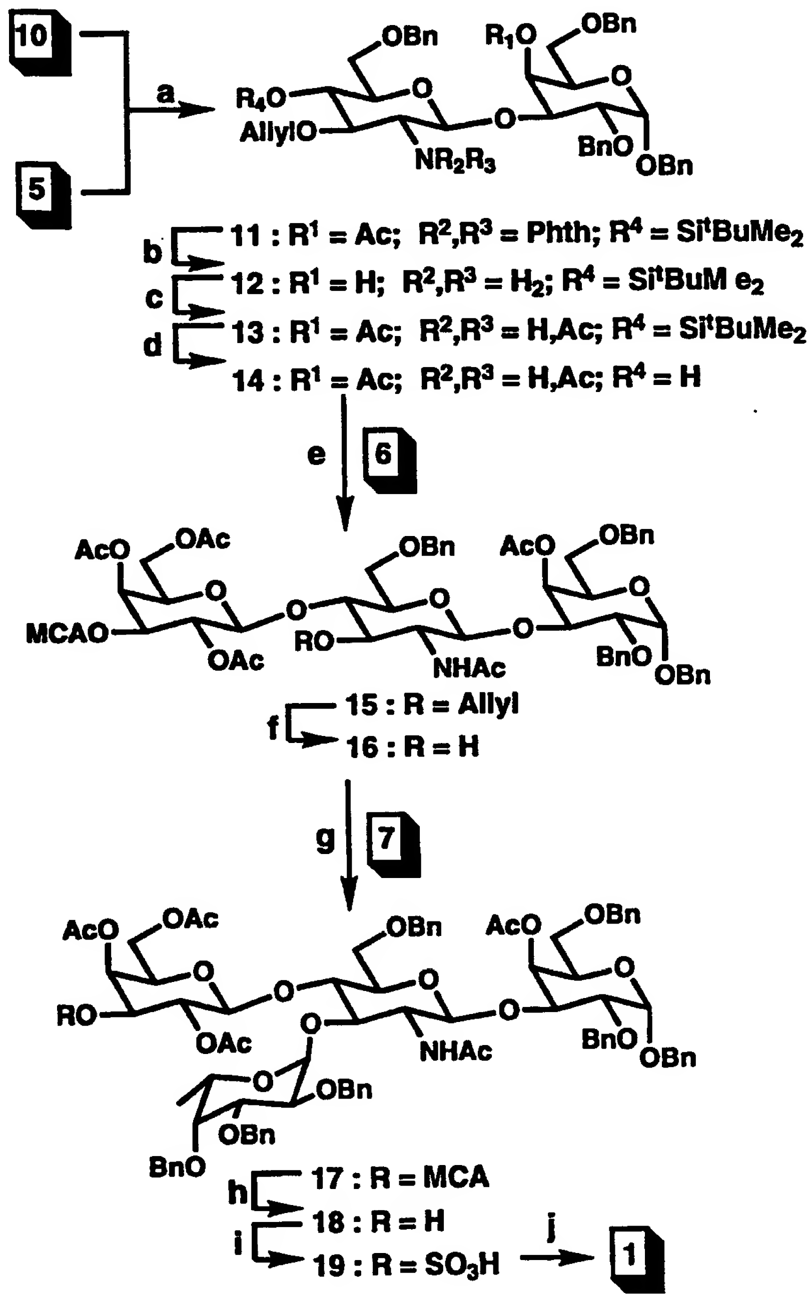
11. A method for making compound 3 comprising the following steps:

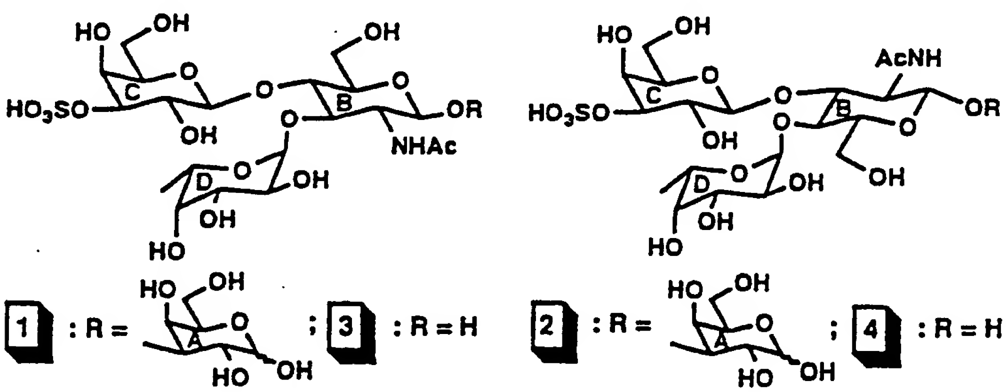


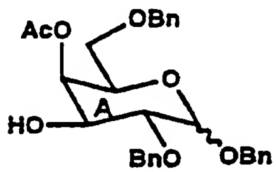
12. A method for making compound **2** comprising the following steps:



13. A method for making compound 1 comprising the following steps:

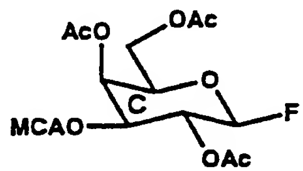






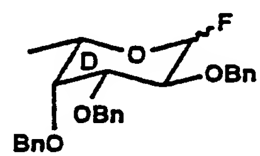
[from D-galactose]

5



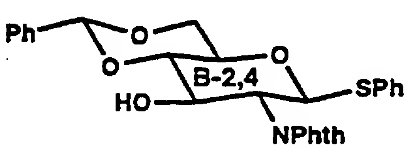
[from D-galactose]

6



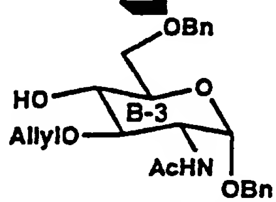
[from L-fucose]

7



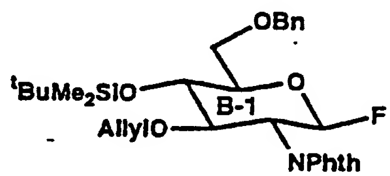
[from D-glucosamine]

8



[from D-glucosamine]

9



[from D-glucosamine]

10

Ac = acetyl; Bn = benzyl; MCA = chloroacetyl; Phth = phthaloyl

Figure 1. Sulfated Lewis^{x} (1,3) and Lewis^{a} (2,4) target molecules and key intermediates (5-10) for their chemical synthesis .

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 94/10790

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H15/18 C07H13/04 C07H3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARBOHYDRATE RESEARCH, vol.144, 1985, AMSTERDAM NL pages 45 - 55 PAULSEN H. ET AL. 'Entwicklung eines syntheseblocks der 3-O-beta-D-Galactopyranosyl-D-galactopyranose' see pages 47 and 50 ---	1
X	CARBOHYDRATE RESEARCH, vol.226, 1992, AMSTERDAM NL pages 91 - 100 JAIN R.K. AND MATTA K.L. 'Synthesis of oligosaccharides containing the X-antigenic trisaccharide (alpha-L-Fucp-(1-3)-[beta-D-Galp-(1-4)]-beta-D-GlcpNAc) at their nonreducing ends' see pages 92 and 95 ---	5

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 1995	02.02.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Day, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 416 396 (MERCK PATENT GMBH) 13 March 1991 see example 18	3
A	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1991, LETCHWORTH GB pages 870 - 872 NICOLAOU K.C. ET AL. 'Stereocontrolled Synthesis of Sialyl Lex, the Oligosaccharide Binding Ligand to ELAM-1 (Sialyl = N-acetylneuramin)' cited in the application see the whole document	1-13
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.114, 1992, WASHINGTON, DC US pages 3126 - 3128 NICOLAOU K.C. ET AL. 'Total synthesis of Sialyl Dimeric Lex' cited in the application see the whole document	1-13
A	JOURNAL OF BIOLOGICAL CHEMISTRY, vol.267, no.33, 25 November 1992, BALTIMORE, MD US pages 23806 - 23814 CHANDRASSEKARAN E.V. ET AL. 'Ovarian Cancer alpha 1,3-L-Fucosyltransferase' cited in the application see page 23807	11
A	BIOCHEMISTRY, vol.31, 1992, EASTON, PA US pages 9126 - 9131 YUEN C.-T. ET AL. 'Novel Sulfated Ligands for the Cell Adhesion Molecule E-Selectin Revealed by the Neoglycolipid Technology among O-Linked Oligosaccharide on an Ovarian Cystadenoma Glycoprotein' cited in the application see abstract	12,13
P,X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.115, no.19, 22 September 1993, WASHINGTON, DC US pages 8843 - 8844 NICOLAOU K.C. ET AL. 'Total Synthesis of Sulfated Lex and Lea-Type Oligosaccharide Selectin Ligands' see the whole document	1-13

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/10790

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0416396	13-03-91	DE-A- 3929295	07-03-91
		AU-A- 6212090	07-03-91
		CA-A- 2024485	05-03-91
		HU-B- 207337	29-03-93
		JP-A- 3093792	18-04-91